equivalents per dose.

Remarks

Reconsideration and allowance are respectfully requested.

Claims 1-10, and 12-24, are pending and are at issue. Claims 1, 12, 16, and 18 have been amended. Claim 24 has been added.

Support for the amendment of claims 1, 12, 16, and 18, and the addition of the new claim 24 can be found on page 15, lines 25-32. No new matter has been added by the amendment of claims 1, 12, 16, and 18, or by the addition of claim 24.

1. Sequence Listing

In response to the Notice To Comply With Requirements For Patent Applications Containing Nucleotide And/Or Amino Acid Sequence Disclosures, a copy of which is enclosed, please amend the specification to include the enclosed Sequence Listing, submitted in both computer readable form and a paper copy.

2. Oath/Declaration

A Supplemental Declaration is enclosed, claiming priority based upon the provisional patent application No. 60/084,081, filed May 4, 1998.

3. Double Patenting and Obviousness Rejections

The Examiner has provisionally rejected claims 1-23 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over U.S. Patent No. 5,290,551 to Berd (hereinafter "Berd"), in view of U.S. Patent No. 5,478,556 to Elliot et al. (hereinafter "Elliot"). The Examiner has also rejected claims 1-23 as allegedly obvious over Berd in view of Elliot. Because both rejections are obviated by the same line of evidence and argument, they are addressed together.

The Examiner argues that the claims are not patentably distinct from claims 1 and 2 of Berd, taken in view of Elliot. Elliot describes cancer vaccination protocols consisting of weekly administrations of tumor-associated antigens together with various adjuvants.

Because there is no motivation to combine Berd with Elliot as advanced by the Examiner, and indeed because there is a teaching away from this combination, the rejections are respectfully traversed, and reconsideration is requested.

Berd discloses and, in claim 1, claims a melanoma vaccine comprising haptenized autologous melanoma cells and an immunological adjuvant, the administration of which can be preceded by a low dose cyclophosphamide injection, as described in claim 2. Further, the disclosure of Berd teaches an optional vaccination protocol consisting of monthly administrations of the vaccine. Claims 1 and 18 of this application have been amended to recite the composition comprises a maximum of 7.5×10^6 cells or cell equivalents (c.e.) extract per dose of an isolated hapten modified human tumor cell or cell extract. Berd does not teach this dosage range, or the dosages of claims 16 (as amended) and new claim 24.

Elliot fails to supply the missing teaching. There is no disclosure in Elliot of immune therapy with a haptenized tumor cell or tumor cell extract vaccine. On the contrary, Elliot

B

Elliot fails to supply the missing teaching. There is no disclosure in Elliot of immune therapy with a haptenized tumor cell or tumor cell extract vaccine. On the contrary, Elliot discloses and claims treatment with a tumor associated antigen (see, *e.g.*, claim 1) carefully extracted by a hypotonic extraction procedure (see Elliot, col. 3, ll. 17-23 and Figure 1). Thus, this reference pursues an entirely different avenue of tumor therapy than that described in Berd. Accordingly, there is no basis, absent hindsight gained from the instant application, to combine the teachings of Elliot with those of Berd. However, the Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 USPQ 2d 1780, 1784 (Fed. Cir. 1992). On the contrary, the references diverge and lead away from each other: one towards high doses of haptenized whole tumor cells administered every four weeks; the other towards weekly administration of a purified tumor antigen. Where references so diverge, obviousness does not obtain. *In re Lundsford*, 148 USPQ 721, 726 (CCPA 1966); *See In re Gurley*, 31 USPQ 2d 1130, 1131 (Fed. Cir. 1994), *In re Bell*, 26 USPQ 2d 1529, 1532 (Fed. Cir. 1993).

In particular, Applicant takes issue with the Examiner's unsupported contention that one of ordinary skill in the art, familiar with Berd, would be at all inclined to modify Berd by administering the vaccine weekly, as allegedly suggested by Elliot. There is simply no ground on which to base such a combination, given the objective differences between the references: Berd describes a haptenized tumor cell composition of at least 10^7 cells per dose and method of immunotherapy, while Elliot describes a purified antigen vaccine and therapy. Berd discloses administration with BCG, which is a potent adjuvant that typically elicits an uncomfortable localized inflammatory response, which would clearly argue against weekly administration. The composition and method disclosed by Berd were effective, thus precluding

B

any motivation to modify them. The Examiner provides no motive or incentive that might constitute the objective teaching necessary to overcome problems of weekly administrations expected from a BCG vaccine, or to reduce an effective concentration. The Federal Circuit has clearly stated that the Examiner must show some objective teaching from the references that would lead one to combine them; the mere fact that the references may be so modified is not sufficient. *See Fritch*, 23 USPQ 2d 1780, 1783-4.

Even were the references to be combined, the lower dose administration set forth in this application (a maximum of 7.5×10^6 cells per dose), which is significantly lower than the range of 10^7 to 2.5×10^7 set forth in Berd, nevertheless surprisingly has as robust a protective effect. Indeed, the lower dosages set forth in this application provide the added advantage of increasing the total number of administrations possible, a feature not in the least suggested by the references of record.

Thus, the references fail to suggest the clear advantages of the claimed methods and compositions as shown in Example 15; weekly administration of the haptenized tumor cells was as effective or more effective than set forth in Berd (59% DTH response with weekly administration over 6 weeks compared to a 45% response following the Berd protocol). As the specification points out, "the dosage and schedule of administration of human tumor vaccines may be important inducing immunological responses that have clinical meaning" (specification, page 53, lines 23-24). Neither Berd nor Elliot teach the importance of these factors in eliciting a more effective anti-tumor response, much less the advantageous dosage and schedule disclosed and claimed herein.

B

4. Clarity of the Claims

The Examiner has rejected claims 1-23 under 35 U.S.C. § 112, second paragraph, alleging that the claims are unclear in their recitation of "a therapeutically effective amount"; that they fail to define "QS-21"; and that they fail to define the meaning of "c.e."

In response, Applicant has amended claims 1 and 18 to recite that the vaccine elicits an antitumor response when administered with an adjuvant (as set forth in the specification at page 10, lines 18-21) in lieu of a therapeutically effective amount. In addition, the term "c.e." has been spelled out as "cell equivalents", as set forth in the specification at page 15, line 17.

Applicant takes issue with the Examiner's contention that the term QS-21 is not well known in the art. On the contrary, this adjuvant compound is very well known, *e.g.*, as disclosed in U.S. Patent No. 5,057,540; see U.S. Patent No. 5,723,130 to Hancock et al., *e.g.*, at col. 2, ll. 65-67 and col. 3, ll. 1-7 [referencing U.S. Patent No. 5,057,540] ; and U.S. Patent No. 5,612,030 Chatterjee et al., *e.g.*, at col. 11, ll. 20-22; both of which patents claim compositions containing QS-21 (copies enclosed at Tabs 1, 2 and 3, respectively).

In view of the foregoing amendments and remarks, Applicant submits that the claims particularly point out and distinctly claim the invention. Accordingly, the rejection under 35 U.S.C. § 112, second paragraph should be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks in the file history of this application is requested. The claims as amended meet the statutory criteria for patentability, and

B

are believed to be in conclusion for allowance. The Examiner is invited to contact the undersigned by telephone if any issues are found. Allowance of the application is earnestly solicited.

Respectfully submitted,

By _____

Paul F. Fehlner, Ph.D.
Reg. No. 35,135
Attorney for Applicant(s)

Dated: February 1, 2000

DARBY & DARBY P.C.
805 Third Avenue
New York, New York 10022
212-527-7700

M:\1225\1E251\AL0168.WPD

B